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NOTIFICATION CONCERNING
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APPLICATION AS PUBLISHED OR REPUBLISHED

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Applicant

UNIVERSITEIT GENT et al

The International Bureau transmits herewith the following documents:

☐ copy of the international application as published by the International Bureau on under No. WO

☑ copy of international application as republished by the International Bureau on 20 October 2005 (20.10.2005) under No. WO 2005/033694
For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48) or (88) *(as the case may be)* on the front page of the attached document.

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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL ANTISENSE OLIGOMERS AND USE THEREOF

(57) Abstract: The invention relates to the use of a novel type of antisense oligomers for use in the *in vitro* or *in vivo* inhibition of gene expression of a target gene. These oligomers, called exon-bridging oligomers are complementary to those parts of a spliced mRNA which are derived from two adjacent exons in the primary RNA transcript, and are called exon-bridging antisense oligomers. These oligomers have no complimentarity to genomic DNA. These oligomers can be used to performs antisense inhibition with less aspecific binding to genomic DNA. The exon-bridging oligomers are suitable for inhibiting Interleukin1 type I Receptor in, for instance, chondrocytes, and are suitable for the prevention or treatment of osteoarthritis.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N31/00 A01N43/00 A61K31/70 C07H21/02 C07H21/04
C07H21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, Sequence Search, BIOSIS, MEDLINE, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MIRAGLIA L ET AL: "INHIBITION OF INTERLEUKIN-1 TYPE I RECEPTOR EXPRESSION IN HUMAN CELL-LINES BY AN ANTISENSE PHOSPHOROTHIOATE OLIGODEOXYNUCLEOTIDE" INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, ELMSFORD,NY, US, vol. 18, no. 4, 1996, pages 227-240, XP001002842 ISSN: 0192-0561 Abstract; Experimental procedures; p. 228, under "cell culture and oigonucleotide treatment of cells and Analysis of IL-1 receptor, type 1 and ICAM-1 mRNA levels; Table 1 p.230; Discussion.	1-19,36, 37

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 February 2005	13. 09. 05

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bretherick, J

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 856 099 A (MIRAGLIA ET AL) 5 January 1999 (1999-01-05) Columns 1 and 2, Examples 1-5, Table 1; Example 6-9.	1-19,36, 37
Y	BURCH R M ET AL: "OLIGONUCLEOTIDES ANTISENSE TO THE INTERLEUKIN 1 RECEPTOR MRNA BLOCKTHE EFFECTS OF INTERLEUKIN 1 IN CULTURED MURINE AND HUMAN FIBROBLASTS AND IN MICE" JOURNAL OF CLINICAL INVESTIGATION, NEW YORK, NY, US, vol. 88, October 1991 (1991-10), pages 1190-1196, XP000925602 ISSN: 0021-9738 Abstract; p.1191, RH column, 2nd paragraph;Figs. 1 and 2; Discussion, esp. 1st 3 paragraphs.	1-19,36, 37
Y	DEMOOR J M ET AL: "ANTISENSE NUCLEIC ACIDS TARGETED TO THE THYMIDYLATE SYNTHASE (TS) MRNA TRANSLATION START SITE STIMULATE TS GENE TRANSCRIPTION" EXPERIMENTAL CELL RESEARCH, SAN DIEGO, CA, US, vol. 243, 1998, pages 11-21, XP002923758 ISSN: 0014-4827 Introduction, Fig. 1; Results 1 1st paragraph; paragraph bridging pp. 14 and 15; p 18, LH column, 2nd sentence.	1-19,36, 37

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5856099 A	05-01-1999	AU 2993397 A	09-12-1997
		EP 0928419 A1	14-07-1999
		WO 9744656 A1	27-11-1997

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BE2004/000142

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-19, 36, 37

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-19, 36,37

In vitro method for increasing the synthesisof extracellular matrix compounds in a cell population by inhibiting the expression if IL-1R1 characterised in that it comprises the step of contacting the cells with an IL-1R1 exon-bridging antisense oligomer; antisense oligomers for this purpose; their use in the preparation of medicaments.

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2. claims: 20-35

Methods for the in vitro modulation of the expression of a target gene in a cell population with an antisense oligomer characterised in that mature mRNA function is inhibited by contacting the cells with an exon-bridging antisense oligomer directed against said mature mRNA; method of producing an exon-bridging antisense oligomer for the inhibition of expression of a target gene.
